CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
SUMMARY OF TOXICOLOGICAL DATA
MEDICAL TOXICOLOGY BRANCH

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CYHEXATIN (Plictran)

SB 950-106, Tolerance # 144

August 6, 1986
Revised November 24, 1986
Revised January 29, 1987
Revised May 27, 1987

I. DATA GAP STATUS

Chronic rat: Data gap, inadequate study, no adverse effect indicated.

Chronic dog: No data gap, no adverse effect

Onco rat: No data gap, possible adverse effect (not onco)

Onco mouse: No data gap, no adverse effect

Repro rat: Data gap, inadequate study, no adverse effect indicated, new study in progress

Terato rat: Data gap, inadequate studies, no adverse effect indicated.

Terato rabbit: No data gap, possible adverse effect

Gene mutation: No data gap, no adverse effect.

Chromosome: No data gap, no adverse effect.

DNA damage: No data gap, no adverse effect.

Neurotox: Not required.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name: 3B>SB106CYX.JRG
Revised file name: SB106CYX.JG2, Nov. 24, 1986
Revised file name: SB106CYX.JG3, Jan. 29, 1987
Revised file name: SB106CYX.JG4, May 27, 1987, FM

II. TOXICOLOGY SUMMARY

CHRONIC, RAT

003 962183 Title: Two-Year Dietary Feeding Studies in rat. (1970, Hine Labs) JW, 4/23/85. Summary; 90/sex/group were fed 3, 6 or 12 mg/kg with some effects on body weight, food consumption and organ/weight ratios at high dose. No individual data, no description of test article, insufficient information to evaluate. Two-page summary.

CHRONIC, DOG

003 962184 Title: Two-Year Dietary Feeding Studies in Dogs. (1970, Hine Labs) JW, 4/23/85. Summary; Unspecified number of dogs were fed 0, 3, or 6 mg/kg/day over 2 years or 12 mg/kg/day for 6 months. One page report. Insufficient information to evaluate.
EPA 1-liner: Supplementary. NOEL $\leq$ 3 mg/kg (lowest level tested) (increased heart, liver, spleen and kidney weights, reduced copper content of urine K+ increased, Na+ decreased in urine, SAP increased.)

** 024 050737 Title: Cyhexatin: Results of a One-year Dietary Toxicity Study in Beagle Dogs. (Dow, 7/3/86, Report HET K-053361-021) JG, 1/23/87. Cyhexatin, 95%; fed in the diet for one year to 6/sex/group at 0, 0.25, 0.5 or 0.75 mg/kg/day (dose selection based on earlier studies); NOEL = 0.5 mg/kg/day

(body weight gain, increased organ weights for heart, liver, kidneys with no histopathological findings reported). Acceptable. Although this study showed marginal toxicity at the high dose of 0.75 mg/kg/day, earlier subchronic studies indicated a NOEL $\leq$ 0.75 mg/kg based on increased heart weight and palatability of the diet.

ONCOGENICITY, RAT

** **010 962185** Title: Results of a Two-Year Chronic Toxicity Study of Tricyclohexyltin Hydroxide Administered to Rats by the Dietary Route. (9/26/1977, Dow) JW, 4/23/85 and JG, 1/23/87. Adequate study with 50/sex/group fed 0, 1, 3 or 6 mg/kg/day at 98.6% purity. Decreased body weight gain at 3 and 6 mg/kg. Adverse effects noted were bile duct hyperplasia at all treatment levels, hepatocellular alteration at high dose in both sexes; degenerative myopathy in high dose group, and radiculomyelopathy of the spinal cord in high dose females and mid dose males. Sys NOEL < 1 mg/kg/day (bile duct hyperplasia), onco NOEL $\geq$ 6 mg/kg/day. Study is not acceptable as a chronic or combined due to lack of hematology, clinical chemistry and urinalysis.

EPA 1-liner: Minimum. Oncogenic NOEL > 6 mg/kg/day (HDT); Systemic NOEL < 1 mg/kg/day (LDT) (bile duct hyperplasia, hepatocellular alterations and body weight depression.)

023 050736 (4 volumes) Supplement to 962185 with individual data.

018 036094 (1977, Dow) Duplicate of 010 962185

029 051515 Title: Data Evaluation Record: Cyhexatin. December 14, 1984. EPA evaluation of 962185.

ONCOGENICITY, MOUSE

** 018 036095 Title: Cyhexatin: Results of a Two-year Dietary Toxicity and Oncogenic Study in Male and Female B6C3F1 Mice. (4/13/1981, Dow, HET-K-53361-(16)) JRG, 4/24/86. Cyhexatin, 98%, was fed to 50/sex/year (plus 10/sex for 1 year sac) at 0, 1, 3 or 6 mg/kg over 2 years. NOEL: 3 mg/kg. No consistent chronic effect reported and no evidence of an onco effect. Inadequate justification of dose and too narrow a range, food consumption only for 20/sex/group, not all. Analysis of diet indicated the content in the two lower dose levels was generally too high so that the exposures were not discrete. Inadequate numbers of samplings of diet early in study when most important. Marginal decrease in male body weight gain at high dose. Decreased food consumption in first month of study in both sexes at high dose - unpalatable. Acceptable with minor variations.
EPA 1-liner: Systemic NOEL = 3 mg/kg (mortality, organ weight data.

025 050738 Individual pathology observations, historical controls and EPA Evaluation Record for 036095. Submission resulted in upgrading study.

029 051516 Title: Data Evaluation Record: Cyhexatin. December 17, 1984. EPA evaluation of 036095.

REPRODUCTION, RAT

019 036099 Title: Dowco 213 Reproduction and Teratology Studies in Rats. (12/1969, Hine Labs, Report No. 66) JRG, 4/24/86. Study done with wettable powder formulation of cyhexatin, no purity given. Ten males and 20 females per group were fed 0, 12.5, 50 or 100 ppm for 3 generations, 2 litters each (plus one each for teratology); no consistent reproductive effect; possible NOEL: 12.5 ppm (repro) (weanling pup weight); 50 ppm (parental body weight). Unacceptable: No diet analysis or purity of test article; no histopath on reproductive organs of parental animals as required; no individual body weights over time; dose selection not justified - the mean body weight of some groups (F0, F2b) of males is >10% lower at sacrifice possibly indicating a mtd is being approached but no other observations are reported. Because no weights over the test period are included, the significance of the pup weight differential at termination cannot be evaluated. No identification of mating pairs, no examination of females for evidence of day of mating so gestation time cannot be assessed (report mentions F3a litters of 100 ppm group were born 3-6 days later than other groups - no data.) Weanling weights showed wide variation among litters/groups/generations. Mean for 100 ppm statistically lower for some but not all and "a" tended to be lighter than "b".
EPA 1-liner: Invalid. Reproductive NOEL = 12.5 ppm (LDT) (reduced offspring weights.)

003 962188 (1969, Hine Labs) JW, 4/23/85. Very brief summary of 019 036099.

Note: A two-generation rat study is in progress for EPA reregistration and is due in September, 1988.

REPRODUCTION, RABBIT

019 036098 Title: Dowco 213 Reproduction and Teratology Studies in Rabbits. (12/1969, Hine Labs, Report No. 65) JRG, 4/23/86. Summary; Study done with wettable powder formulation. Groups of 5, 7 and 5 rabbits were given 0, 0.75 or 3.0 mg/kg by oral gavage, days 8-16 of gestation. Unacceptable - inadequate individual data, no justification of dose, too few animals, others. Each doe was mated twice - once for repro, once for teratology. No adverse effect is reported.
EPA 1-liner: Invalid. NOEL $\geq$ 3 mg/kg (HDT).

003 035752 (1969, Hine Labs) Very brief summary of 019 036098.

TERATOLOGY, RAT

019 036100 Title: Dowco 213 Reproduction and Teratology Studies in Rats. (1969, Hine Labs, Report No. 66) JRG, 4/24/86. Study done with wettable powder formulation . Cyhexatin, no purity stated. Twenty females per group pregnant with their third litters were fed 0, 12.5, 50 or 100 ppm throughout pregnancy. No evidence of teratogenic effect is reported. Possible NOEL: >100 ppm (develop. tox.), 50-100 ppm for maternal body weight. Study mentions artifacts of handling of fetuses. Also, some of F1c were lost in KOH "accidentally". No justification of doses, and no analysis of diet, body weights measured only once, no clinical obs presented. Because diet analysis is missing and the diet was the route of administration, it is difficult to verify a NOEL.
EPA 1-liner: Invalid. Teratogenic NOEL > 100 ppm (HDT.

003 035753 (1969, Hine Labs) JW, 4/23/85. Summary of 019 036100.

022 49854 Title: Cyhexatin: Teratology Study in Rats. (10/17/86, IRDC #133-048) JAP, 11/24/86. Tricyclohexyltin hydroxide, 95.6%; tested at 0, 0.5, 1.0 or 5.0 mg/kg/day, gavage, day 6-15 to 30 Sprague-Dawley rats/dose level; no adverse effect; developmental NOEL > 5.0 mg/kg Unacceptable; No maternal toxicity.
Rebuttal in -006 did not upgrade study (see below). FM, 5/27/87.

006 054072 Title: Cyhexatin: Oral Teratology Probe Study in Sprague-Dawley Rats. (4/8/86, Dow) FM, 5/27/87. Technical cyhexatin, 95.6% pure, by oral gavage in corn oil at 10, 5, 1, or 0 mg/kg/day on days 6-15 to 10/level; transient slight maternal weight gain and feed intake reduction @ 10 or 5 mg/kg, and slight liver weight increase @ 10 mg/kg, NOT evidence of maternal toxicity; no developmental effects, developmental toxicity NOEL>10 mg/kg/day. Submitted by registrant in rebuttal to teratology study, record #49854, above; did not upgrade study.

TERATOLOGY, RABBIT

019 036097 Title: Dowco 213 Reproduction and Teratology Studies in Rabbits. (12/1969, Hine Labs, Report No. 65) JRG 4/23/86 Summary; Study done with wettable powder formulation - see comments under 036098 above.

003 035754 (1969, Hine Labs) JW 4/23/85 Very brief summary of 019 036097.

021 45032 (5/19/86, Dow) JAP, 11/21/86. Letter of prelim. findings from in-progress studies reported in records # 49853 and # 49854.

** **022 49853** Title: Cyhexatin Teratology Study in Rabbits. (10/17/86, IRDC #133-049). JAP, 11/24/86. Tricyclohexyltin hydroxide, 95 - 96 % based on weight per weight; tested at 0, 0.5, 1.0 or 3.0 mg/kg/day, oral gavage, day 7-19 to 20 NZW rabbits/group; maternal NOEL = 1.0 mg/kg/day (abortions), developmental NOEL = 0.5 mg/kg/day (increased resorptions and malformations (hydrocephaly) at 1.0 and 3.0 mg/kg/day). Acceptable. Possible adverse effect.

GENE MUTATIONS

Microbial systems

019 036101 Title: Evaluation of Tricyclohexylhydroxy Stannane in the Ames Salmonella/Mammalian Microsomal Mutagenicity Assay. (8/9/1985, Dow Chemical, HET-K-053361-022) JRG, 4/23/86. Ames Assay. Cyhexatin at 95.6%. Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 were tested with and without rat liver activation at 0, 0.63, 2.0, 6.3, 20, 63 (ppt.) or 200 (ppt.) ug/plate in triplicate, 30 min. preincubation. Mean values given, 1 trial only. All controls are included. Unacceptable (trial number). No evidence for increase in reversion rate is reported.

010 962189 Title: Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Tricyclohexyl Hydroxide (Cyhexatin.) (4/12/1978, Huntington Research, DWC 306/78368) JW, 4/23/85. Ames Assay. Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation were tested at 2, 20, 200 and 2000 ug/plate in triplicate. Cyhexatin technical at 92.2%. Precipitate at 2000 ug. Review states that background revertant values for strains either low or high. These are as

follows: TA98: 48 (-S9), 63 (+S9); TA100: 57 (-S9), 44 (+S9); TA1535: 8 (-S9), 8 (+S9); TA1537: 2 (-S9), 3 (+S9); TA1538: 6 (-S9), 7 (+S9). While these values are low for TA100 and high for TA98, there is no evidence for a mutagenic response. Unacceptable (no repeat trial.)
EPA 1-liner: Provisionally acceptable (repeat TA 100). Reported negative for histidine reversion up to 2000 ug/plate.

SUMMARY: In evaluating these studies, each was found to be unacceptable. No mutagenic activity was found in either study. When the data from the two studies are examined collectively, they provide sufficient evidence that there is no mutagenic activity of cyhexatin in bacterial systems. The data gap can be considered filled.

Mammalian systems

** 025 050741 Title: The Evaluation of Tricyclohexylhydroxy Stannane in the Chinese Hamster Ovary Cell/Hypoxanthine (Guanine) Phosphoribosyl Transferase [CHO/HGPRT] Forward Mutation Assay. (Dow, 7/21/86, HET-K-053361-024) JG, 1/26/87. Cyhexatin, 95.6%; tested without activation at 0, 10, 20, 30, 40 or 50 nM, 4-5 hours incubation; with rat liver activation, at 0, 2, 3, 3.5, 4, 4.5 or 5 uM in trial 1 and at 0, 2.7, 3.2, 3.6, 4.1 or 4.5 uM, trial 2; no significant effect reported; acceptable.

CHROMOSOMAL MUTATIONS

** 019 036103 Title: Evaluation of Cyhexatin in the Mouse Bone Marrow Micronucleus Test. (4/9/1985, Dow Chemical, TXT:K-053361-026) JRG, 4/24/86. Mouse Bone Marrow micronucleus test. Cyhexatin, 95.6%; 5/sex/group were given 10.

0, 18, 60 or 180 mg/kg by oral gavage and sacrificed at 24 or 48 hours; no increase in micronuclei or change in PCE%; no evidence of toxicity. Acceptable but no evidence of toxicity by clinical obs or bone marrow findings.

025 050989 Supplement to 036103 with acute toxicity to justify dose selection. This submission resulted in upgrading of study.

DNA REPAIR/OTHER

**019 036102 Title: Evaluation of Tricyclohexylhydroxy Stannane in the Rat Hepatocyte Unscheduled DNA Synthesis Assay. (7/1/1985, Dow Chemical, HET K-053361-023) JRG, 4/23/86. UDS in rat hepatocytes; cyhexatin, 95.6%. Rat hepatocytes were exposed for 18 hours to 1.6×10^{-8}, 5×10^{-8}, 1.6×10^{-7}, 5×10^{-7} (toxic) 1.6×10^{-6} fand 5×10^{-6} moles/liter
No evidence of UDS is reported. Acceptable.

NEUROTOXICITY, HEN